

WO2005092384

Publication Title:

COMBINATION THERAPY

Abstract:

Abstract of WO2005092384

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of AZD2171 in combination with a platinum anti-tumour agent; to a pharmaceutical composition comprising AZD2171 and a platinum anti-tumour agent; to a combination product comprising AZD2171 and a platinum anti-tumour agent for use in a method of treatment of a human or animal body by therapy; to a kit comprising AZD2171 and a platinum anti-tumour agent; to the use of AZD2171 and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation. Data supplied from the esp@cenet database - Worldwide

Courtesy of <http://v3.espacenet.com>

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 October 2005 (06.10.2005)

PCT

(10) International Publication Number
WO 2005/092384 A2

(51) International Patent Classification⁷: **A61K 45/06**,
31/517, 33/24, 31/282

Robert [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(21) International Application Number:
PCT/GB2005/001079

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-SE-151 85 Sodertalje (SE).

(22) International Filing Date: 22 March 2005 (22.03.2005)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0406450.7 23 March 2004 (23.03.2004) GB
0407755.8 6 April 2004 (06.04.2004) GB

(71) Applicant (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GW, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, MK, ML, MN, MR, MW, MX, MZ, NA, NE, NI, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK only): **ASTRAZENECA AB** [SE/SE]; S-SE-151 85 Sodertalje (SE).

(71) Applicant (for MG only): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **WEDGE, Stephen**

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/092384 A2

(54) Title: COMBINATION THERAPY

(57) Abstract: The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of AZD2171 in combination with a platinum anti-tumour agent; to a pharmaceutical composition comprising AZD2171 and a platinum anti-tumour agent; to a combination product comprising AZD2171 and a platinum anti-tumour agent for use in a method of treatment of a human or animal body by therapy; to a kit comprising AZD2171 and a platinum anti-tumour agent; to the use of AZD2171 and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

COMBINATION THERAPY

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of AZD2171 in combination with a platinum anti-tumour agent; to a pharmaceutical composition comprising AZD2171 and a platinum anti-tumour agent; to a combination product comprising AZD2171 and a platinum anti-tumour agent for use in a method of treatment of a human or animal body by therapy; to a kit comprising AZD2171 and a platinum anti-tumour agent; to the use of AZD2171 and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules

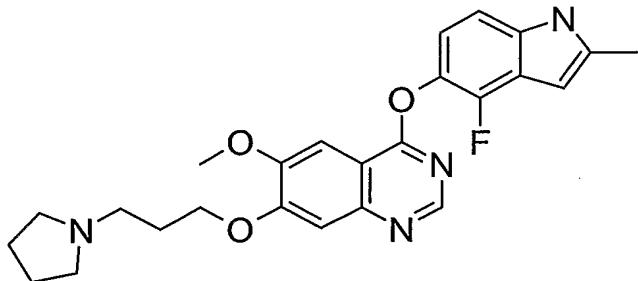
characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt-1 (also referred to as VEGFR-1), the kinase insert domain-containing receptor, KDR (also referred to as VEGFR-2 or Flk-1), and another fms-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., Science (Washington DC), 246: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., Microvasc. Res., 55: 29-42, 1998; Pepper, M.S., Montesano, R., Mandroita, S.J., Orci, L. and Vassalli, J.D., Enzyme Protein, 49: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., (Int. Arch. Allergy Immunol., 107: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. J. Physiol. (Lond.), 533: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which is characteristic of pathological angiogenesis.

It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival, and the induction of vascular permeability (Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H-J., and Dehio, C., EMBO J., 18: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay, D., J. Biol. Chem., 276: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., J. Biol. Chem., 276: 3222-3230, 2001).

Quinazoline derivatives which are inhibitors of VEGF receptor tyrosine kinase are described in International Patent Application Publication No. WO 00/47212. AZD2171 is described in WO 00/47212 and is Example 240 therein. AZD2171 is 4-(4-fluoro-2-methyl-1*H*-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline:

5



AZD2171

AZD2171 shows excellent activity in the *in vitro* (a) enzyme and (b) HUVEC assays 10 that are described in WO 00/47212 (pages 80-83). The AZD2171 IC₅₀ values for inhibition of isolated KDR (VEGFR-2) and Flt-1 (VEGFR-1) tyrosine kinase activities in the enzyme assay were <2 nM and 5 ± 2 nM respectively. AZD2171 inhibits VEGF-stimulated endothelial cell proliferation potently (IC₅₀ value of 0.4 ± 0.2 nM in the HUVEC assay), but does not inhibit basal endothelial cell proliferation appreciably at a > 1250 fold greater concentration (IC₅₀ 15 value is > 500 nM). The growth of a Calu-6 tumour xenograft in the *in vivo* solid tumour model described in WO 00/47212 (page 83) was inhibited by 49%**, 69%*** and 91%*** following 28 days of once-daily oral treatment with 1.5, 3 and 6 mg/kg/day AZD2171 respectively (P **<0.01, P ***<0.0001; one-tailed t test). AZD2171 has been shown to elicit broad-spectrum anti-tumour activity in a range of models following once-daily oral 20 administration.

International Patent Application No. PCT/GB2004/005359 describes AZD2171 maleate salt and states that AZD2171 maleate salt may be applied as a sole therapy or may be used with one or more other substances and/or treatments. A list of other substances is given including platinum derivatives of which cisplatin and carboplatin are named.

25 In WO 00/47212 it is stated that compounds of the invention: "may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by

way of the simultaneous, sequential or separate administration of the individual components of the treatment.”

WO 00/47212 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent.

5 Nowhere in WO 00/47212 is the specific combination of AZD2171 and a platinum anti-tumour agent suggested.

Nowhere in WO 00/47212 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

Unexpectedly and surprisingly we have now found that the particular compound

10 AZD2171 used in combination with a particular selection from the broad description of combination therapies listed in WO 00/47212, namely with a platinum anti-tumour agent, produces significantly better effects than any one of AZD2171 and a platinum anti-tumour agent used alone. In particular, AZD2171 used in combination with a platinum anti-tumour agent produces significantly better effects on solid tumours than any one of AZD2171 and a
15 platinum anti-tumour agent used alone.

A platinum anti-tumour agent is any anti-tumour agent containing platinum. Platinum anti-tumour agents include cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin, satraplatin and AMD473.

In particular a platinum anti-tumour agent is cisplatin.

20 In particular a platinum anti-tumour agent is carboplatin.

In particular a platinum anti-tumour agent is oxaliplatin.

Anti-cancer effects of a method of treatment of the present invention include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include
25 but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. It is expected that when a method of treatment of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer, with or without a solid tumour, said method of treatment will produce an effect, as
30 measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate. Anti-cancer effects include prophylactic treatment as well as treatment of existing disease.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective
5 amount of a platinum anti-tumour agent.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or
10 simultaneously with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum
15 anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously
20 with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective
25 amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or
30 simultaneously with an effective amount of a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective

amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

5 According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-
10 tumour agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.
15

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises
20 administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

25 According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein AZD2171 and a platinum anti-tumour agent
30 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human,

which comprises administering to said animal an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent; wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent, in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent, in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a combination product comprising AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a combination product comprising AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a kit comprising AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent.

According to a further aspect of the present invention there is provided a kit comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof in a first unit dosage form;
- b) a platinum anti-tumour agent in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, in a first unit dosage form;
- b) a platinum anti-tumour agent in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

5 According to a further aspect of the present invention there is provided a kit comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;
- b) a platinum anti-tumour agent together with a pharmaceutically acceptable excipient or
- 10 carrier, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;
- b) a platinum anti-tumour agent together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

20 According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of

25 AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of

30 AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

5 According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of
10 AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a
15 pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the simultaneous, sequential or separate administration of an effective amount of a platinum anti-tumour agent, wherein a platinum anti-tumour agent may optionally be administered together with a pharmaceutically acceptable excipient or carrier, to a warm-blooded animal such as a human in need of such therapeutic treatment.

20 According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, optionally together with a pharmaceutically acceptable excipient or carrier, and the simultaneous, sequential or separate administration of an effective amount of a platinum anti-tumour agent,
25 wherein a platinum anti-tumour agent may optionally be administered together with a pharmaceutically acceptable excipient or carrier, to a warm-blooded animal such as a human in need of such therapeutic treatment.

Such therapeutic treatment includes an antiangiogenic and/or vascular permeability effect, an anti-cancer effect and an anti-tumour effect.

30 A combination treatment of the present invention as defined herein may be achieved by way of the simultaneous, sequential or separate administration of the individual components of said treatment. A combination treatment as defined herein may be applied as a

sole therapy or may involve surgery or radiotherapy or an additional chemotherapeutic agent in addition to a combination treatment of the invention.

Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment with AZD2171 described herein.

5 Other chemotherapeutic agents for optional use with a combination treatment of the present invention include those described in WO 00/47212 which is incorporated herein by reference. Such chemotherapy may cover five main categories of therapeutic agent:

(i) other antiangiogenic agents including vascular targeting agents;

(ii) cytostatic agents;

10 (iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology; and other categories of agent are:

(vi) antisense therapies;

15 (vii) gene therapy approaches; and

(ix) immunotherapy approaches.

Particular examples of chemotherapeutic agents for use with a combination treatment of the present invention are raltitrexed, etoposide, vinorelbine, paclitaxel, docetaxel, gemcitabine, irinotecan (CPT-11) and 5-fluorouracil (5-FU, (including capecitabine)) ; such combinations 20 are expected to be particularly useful for the treatment of cancer of the lung, head and neck, colon, rectum, brain, thyroid, oesophagus, stomach, cervix, ovary, skin, breast, bladder and pancreas.

The administration of a triple combination of AZD2171, a platinum anti-tumour agent and ionising radiation may produce effects, such as anti-tumour effects, greater than those 25 achieved with any of AZD2171, a platinum anti-tumour agent and ionising radiation used alone, greater than those achieved with the combination of AZD2171 and a platinum anti-tumour agent, greater than those achieved with the combination of AZD2171 and ionising radiation, greater than those achieved with the combination of a platinum anti-tumour agent and ionising radiation.

30 According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective

amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as 5 a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for 10 the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

15 According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously 20 with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective 25 amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a 30 pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or

5 simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for

10 the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising

15 radiation, wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically

20 acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for

25 the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour

30 agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human,

which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour agent may each 5 optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or 10 simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and a platinum anti-tumour agent may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the use of 15 AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of 20 AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of 25 AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of 30 AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

- 5 According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.
- 10 According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of a platinum anti-tumour agent, optionally together with a pharmaceutically acceptable excipient or carrier
- 15 and the administration of an effective amount of ionising radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, a platinum anti-tumour agent and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

- According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of a platinum anti-tumour agent, optionally together with a pharmaceutically acceptable excipient or carrier and the administration of an effective amount of ionising
- 25 radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, a platinum anti-tumour agent and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

- A warm-blooded animal such as a human which is being treated with ionising radiation means a warm-blooded animal such as a human which is treated with ionising
- 30 radiation before, after or at the same time as the administration of a medicament or combination treatment comprising AZD2171 and a platinum anti-tumour agent. For example said ionising radiation may be given to said warm-blooded animal such as a human within the period of a week before to a week after the administration of a medicament or combination

treatment comprising AZD2171 and a platinum anti-tumour agent. This means that AZD2171, a platinum anti-tumour agent and ionising radiation may be administered separately or sequentially in any order, or may be administered simultaneously. The warm-blooded animal may experience the effect of each of AZD2171, a platinum anti-tumour agent 5 and radiation simultaneously.

According to one aspect of the present invention the ionising radiation is administered before one of AZD2171 and a platinum anti-tumour agent or after one of AZD2171 and a platinum anti-tumour agent.

According to one aspect of the present invention the ionising radiation is administered 10 before both AZD2171 and a platinum anti-tumour agent or after both AZD2171 and a platinum anti-tumour agent.

According to one aspect of the present invention AZD2171 is administered to a warm-blooded animal after the animal has been treated with ionising radiation.

According to another aspect of the present invention the effect of a method of 15 treatment of the present invention is expected to be at least equivalent to the addition of the effects of each of the components of said treatment used alone, that is, of each of AZD2171 and a platinum anti-tumour agent used alone or of each of AZD2171, a platinum anti-tumour agent and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of 20 treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of AZD2171 and a platinum anti-tumour agent used alone or of each of AZD2171, a platinum anti-tumour agent and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of 25 treatment of the present invention is expected to be a synergistic effect.

According to the present invention a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination 30 treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with AZD2171 or a platinum anti-tumour agent or ionising radiation alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not

respond (or responds poorly) to AZD2171 or a platinum anti-tumour agent or ionising radiation alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of AZD2171 or a platinum anti-tumour agent or ionising radiation may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

As stated above the combination treatments of the present invention as defined herein are of interest for their antiangiogenic and/or vascular permeability effects. Angiogenesis and/or an increase in vascular permeability is present in a wide range of disease states including cancer (including leukaemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, lymphoedema, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including age-related macular degeneration. Combination treatments of the present invention are expected to be particularly useful in the prophylaxis and treatment of diseases such as cancer and Kaposi's sarcoma.

Combination treatments of the present invention may be used to treat cancer, particularly a cancer involving a solid tumour. In particular such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, brain, thyroid, pancreas, bladder, breast, prostate, lungs and skin. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours in colorectal cancer and in lung cancer, for example mesothelioma and non-small cell lung cancer (NSCLC). More particularly such combination treatments of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, multiple myeloma and lymphoma and also, for example, to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and

spread, including for example, certain tumours of the colon (including rectum), brain, thyroid, pancreas, bladder, breast, prostate, lung, vulva, skin and particularly NSCLC.

In another aspect of the present invention AZD2171 and a platinum anti-tumour agent, optionally with ionising radiation, are expected to inhibit the growth of those primary and
5 recurrent solid tumours which are associated with VEGF especially those tumours which are significantly dependent on VEGF for their growth and spread.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous,
10 subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other
embodiments of the present invention the AZD2171 of the combination treatment may be
15 delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. Preferably AZD2171 is administered orally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients. The compositions of the present invention are
advantageously presented in unit dosage form.

20 AZD2171 will normally be administered to a warm-blooded animal at a unit dose within the range 1-50mg per square metre body area of the animal, for example approximately 0.03-1.5 mg/kg in a human. A unit dose in the range, for example, 0.01-1.5mg/kg, preferably 0.03-0.5mg/kg is envisaged and this is normally a therapeutically-effective dose. A unit dosage form such as a tablet or capsule will usually contain, for example 1-50mg of active
25 ingredient. Preferably a daily dose in the range of 0.03-0.5mg/kg is employed.

Platinum anti-tumour agents may be dosed according to known routes of administration and dosages.

For example cisplatin may be administered as a single intravenous infusion over a period of 6-8 hours at a dose of 40-120mg/m² every 3-4 weeks. Alternatively for example
30 cisplatin may be administered as a single intravenous infusion over a period of 6-8 hours at a dose of 15-20mg/m² daily for up to 5 days every 3-4 weeks.

For example carboplatin may be administered as a single short-term intravenous infusion over a period of 15-60 minutes at a dose of 250-400mg/m² every 4 weeks.

For example oxaliplatin may be administered by intravenous infusion over a period of 2-6 hours at a dose of about 85mg/m² every 2 weeks.

The size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the 5 host treated, the route of administration and the severity of the illness being treated.

Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

Radiotherapy may be administered according to the known practices in clinical 10 radiotherapy. The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of γ -rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks.

15 Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-life 20 of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

As stated above the size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is 25 treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

The present invention relates to combinations of a platinum anti-tumour agent with AZD2171 or with a salt of AZD2171. A particular salt is an AZD2171 maleate salt.

30 In particular the present invention relates to combinations of a platinum anti-tumour agent with a form of the AZD2171 free base.

Salts of AZD2171 for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of AZD2171 and its pharmaceutically acceptable salts. Pharmaceutically acceptable salts may, for example, include acid addition salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt and an alkaline earth metal salt such as a calcium or magnesium salt.

AZD2171 may be synthesised according to the processes described in WO 00/47212, in particular those described in Example 240 of WO 00/47212.

AZD2171 maleate salt may be synthesised according to the processes described in International Patent Application No. PCT/GB2004/005359.

15 Platinum anti-tumour agents are commercially available.

The following tests may be used to demonstrate the activity of AZD2171 in combination with a platinum anti-tumour agent.

Human lung cancer (NSCLC) xenograft model (Calu-6)

20 Athymic nude mice are injected subcutaneously (s.c.) with Calu 6 human tumour cells. Treatment begins after 10 days when tumours are established (tumour volume = 350-400 mm³). Groups of animals (n = 9-10 per group) are randomized to receive a single treatment with cisplatin (4 mg/kg intraperitoneally (i.p.)) on day 1 of randomisation, or treatment with AZD2171 (0.5mg/kg or 1.5mg/kg, orally (p.o.) daily) for the duration of the experiment, or 25 drug vehicles only. An additional group of animals (n = 9-10) receives a combination of cisplatin and AZD2171, using the same doses and schedules as used for single agent treatment. On days where animals received both AZD2171 and cisplatin the cisplatin was administered 2 hours after oral dosing with AZD2171.

Animals in all groups are sacrificed when the control tumours reach approximately 2.0 cm³. Tumour size is assessed throughout the experiment by using caliper measurements.

Antitumour effects are determined by comparing tumour growth in the drug-treated groups with tumour growth in the vehicle treated groups. Additionally, the effects of combination treatment are assessed by comparing tumour growth in the group of animals receiving

- 20 -

cisplatin plus AZD2171 with the tumour growth in the groups where animals received single agent therapy alone.

Statistical significance was evaluated using a one-tailed two-sample t-test.

The results are shown in Figures 1 and 2.

- 5 The growth of the tumours was inhibited significantly more by the combination of the two agents AZD2171 (1.5 or 0.5mg/kg) and cisplatin (4mg/kg on day of randomisation) than by either agent alone at the same doses.

CLAIMS

1. Use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in
5 the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.
2. Use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in
10 the production of an anti-cancer effect in a warm-blooded animal such as a human.
3. Use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in
the production of an anti-tumour effect in a warm-blooded animal such as a human.
15
4. Use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in
the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.
20
5. Use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in
the production of an anti-cancer effect in a warm-blooded animal such as a human which is
being treated with ionising radiation.
25
6. Use of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent in the manufacture of a medicament for use in
the production of an anti-tumour effect in a warm-blooded animal such as a human which is
being treated with ionising radiation.
30
7. Use according to any one of claims 1-6 wherein AZD2171 is in a form of the free base.

8. Use according to any one of claims 1-7 wherein the platinum anti-tumour agent is cisplatin.
9. Use according to any one of claims 1-7 wherein the platinum anti-tumour agent is
5 carboplatin.
10. Use according to any one of claims 1-7 wherein the platinum anti-tumour agent is oxaliplatin.
- 10 11. Use of AZD2171 maleate salt and oxaliplatin in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.
12. Use of AZD2171 maleate salt and oxaliplatin in the manufacture of a medicament for
15 use in the production of an anti-cancer effect in a warm-blooded animal such as a human.
13. Use of AZD2171 maleate salt and oxaliplatin in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.
- 20 14. Use of AZD2171 maleate salt and oxaliplatin in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.
15. Use of AZD2171 maleate salt and oxaliplatin in the manufacture of a medicament for
25 use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.
16. Use of AZD2171 maleate salt and oxaliplatin in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human
30 which is being treated with ionising radiation.

17. A pharmaceutical composition which comprises AZD2171, or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, and a platinum anti-tumour agent, in association with a pharmaceutically acceptable excipient or carrier.

5 18. A kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and a platinum anti-tumour agent.

19. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to
10 said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent.

20. A method for the production of an antiangiogenic and/or vascular permeability
15 reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof excluding an AZD2171 maleate salt, before, after or simultaneously with an effective amount of a platinum anti-tumour agent and before, after or simultaneously with an effective amount of ionising radiation.

20

21. A method according to claim 19 or claim 20 wherein AZD2171 is in a form of the free base.

22. A method according to any one of claims 19-21 wherein the platinum anti-tumour
25 agent is oxaliplatin.

23. A method according to any one of claims 19-21 wherein the platinum anti-tumour agent is cisplatin.

30 24. A method according to any one of claims 19-21 wherein the platinum anti-tumour agent is carboplatin.

25. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 maleate salt before, after or simultaneously with an effective amount of oxaliplatin.

5

26. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 maleate salt before, after or simultaneously with an effective amount of oxaliplatin and before, after or simultaneously with an effective
10 amount of ionising radiation.

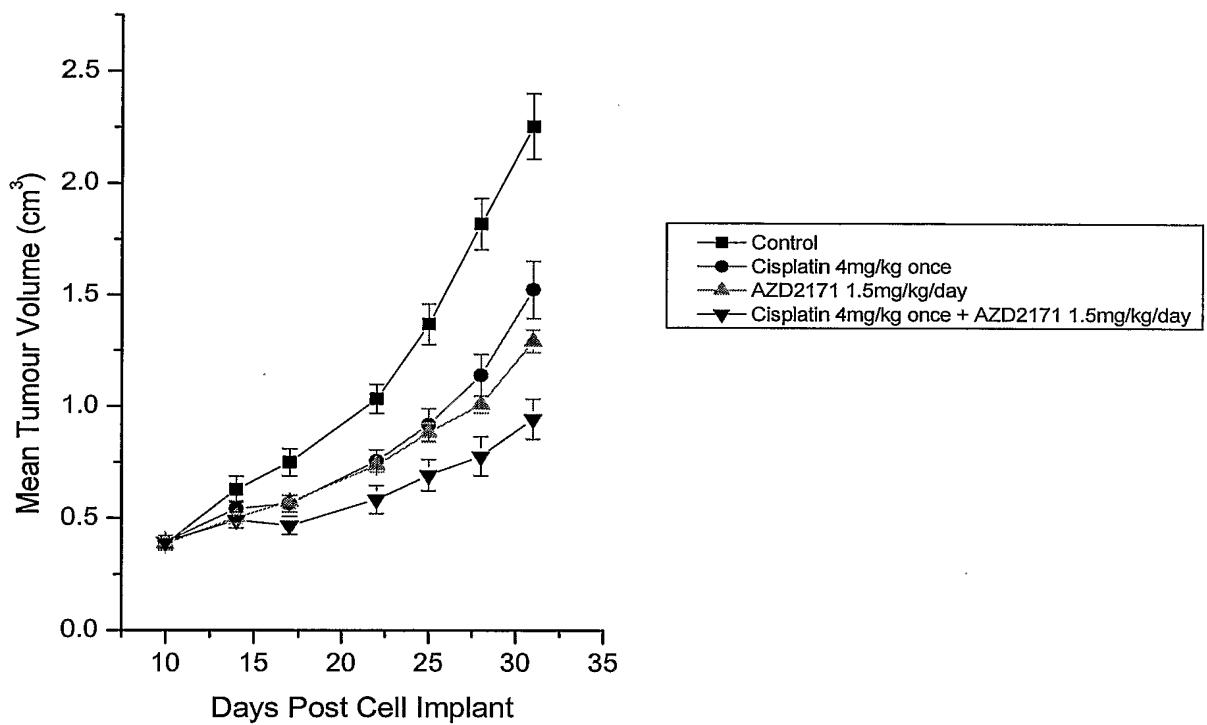


Figure 1

Cisplatin 4mg/kg vs Cisplatin 4mg/kg + AZD2171 1.5mg/kg p=0.0003

AZD2171 1.5mg/kg vs Cisplatin 4mg/kg + AZD2171 1.5mg/kg p=0.0014

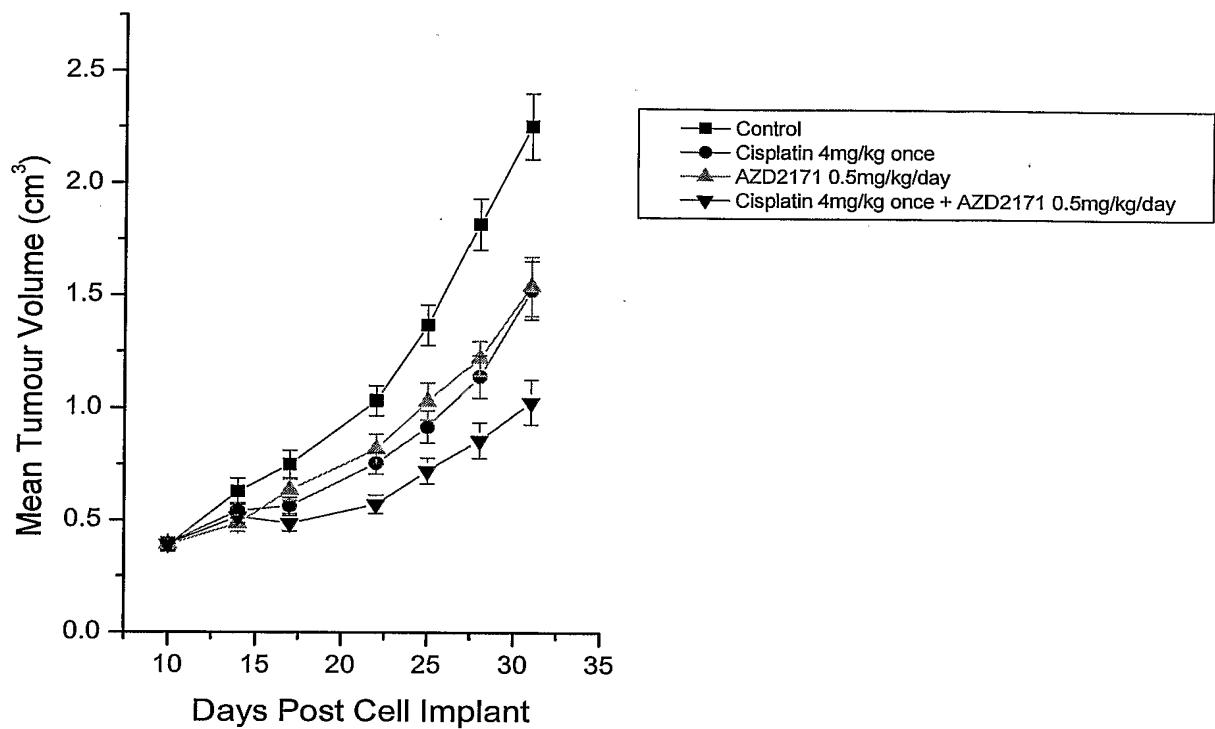


Figure 2

Cisplatin 4mg/kg vs Cisplatin 4mg/kg + AZD2171 0.5mg/kg p=0.0087

AZD2171 0.5mg/kg vs Cisplatin 4mg/kg + AZD2171 0.5mg/kg p=0.0029